

Marked-Up Version To Show Changes Made

In the Specification:

Please replace the paragraph beginning at page 1, line 3, with the following replacement paragraph:

--This application claims benefit under 35 USC §119 of provisional application USSN 60/239,924 filed on October 13, 2000 and of provisional application USSN 60/283,296 filed April 12, 2001, and claims benefit under 35 USC §120 of USSN [90/910,813] 09/910,813 which are hereby incorporated by reference in their entirety for all purposes.--

Please replace the paragraph beginning at page 3, line 6 with the following replacement paragraph:

--The present invention provides purified and isolated polynucleotide molecules that encode polypeptides of the ramoplanin biosynthetic pathway in microorganisms. In one form of the invention, polynucleotide molecules are selected from the contiguous DNA sequence (SEQ ID NO: 1) representing the full-length locus of the ramoplanin biosynthetic pathway and containing the [34] 33 ORFs encoding the proteins forming the ramoplanin gene cluster. The amino acid sequence of the proteins is provided in SEQ ID NOS: 2 to 34. Structural and functional characterization is provided for the [32] 33 ORFs.--

Please replace the paragraph beginning at page 3, line 21 with the following replacement paragraph:

--Certain embodiments of the invention specifically exclude one or more of ORFs 1 to [32] 33, most notably ORFs 1, 2, 3, 6, 7, 8, 20, [221] 21, 27, 28, 31 and 32 (SEQ ID

NOS: 2, 3, 4, 7, 8, 9, 21, 22, 28, 29, 32 and 33) although other ORFs can be excluded without departing from the scope of the invention. Thus, another embodiment of the invention provides an isolated nucleic acid comprising a nucleic acid sequence selected from the group consisting of: (a) a nucleic acid encoding any of ramoplanin ORFs 4, 5, 9 to 19, 22 to 26, 29, 30 and 31 (SEQ ID NOS: 5, 6, 10 to 20, 23 to 27, 30, 31 and 32); (b) a nucleic acid encoding a polypeptide encoded by any of ramoplanin ORFs 4, 5, 9 to 19, 22 to 26, 29, 30 and 31 (SEQ ID NOS: 5, 6, 10 to 20, 23 to 27, 30, 31 and 32); and (c) a nucleic acid encoding a polypeptide that is at least 75%, preferably 80%, more preferably 85%, still more preferably 90% and most preferably 95% or more identical in amino acid sequence to a polypeptide of ramoplanin ORFs 4, 5, 9 to 19, 22 to 26, 29, 30 and 31 (SEQ ID NOS: 5, 6, 10 to 20, 23 to 27, 30, 31 and 32).--

Please replace the paragraph beginning at page 4, line 1, with the following replacement paragraph:

--In one embodiment preferred nucleic acids encode at least two, more preferably three, still more preferably four, or most preferably or more ORFs selected from ORFs 1 to [32] 33 (SEQ ID NOS: 2 to [33] 34) of the ramoplanin locus. In one embodiment, combinations of ORFs selected from ORFs 1 through [32] 33 (SEQ ID NOS 2 to [33] 34) are provided which encode polypeptides that form at least the depsipeptide core structure of ramoplanin. In another embodiment combinations of ORFs selected from ORFs 1 through [32] 33 (SEQ ID NOS: 2 to [33] 34) are provided which encode polypeptides that form at least the fatty-acid side chain of the depsipeptide core structure of ramoplanin. In another embodiment, combinations of ORFs selected from ORFs 1 through [32] 33 (SEQ ID NOS: 2 to [33] 34) are provided which encode polypeptides responsible for the synthesis of 4-hydroxyphenylglycine (HPG) of ramoplanin. In another embodiment, combinations of ORFs selected from ORFs 1 through [32] 33 (SEQ ID NOS: 2 to [33] 34) are provided that encode polypeptides that form at least the beta-hydroxyasparagine residue. In another embodiment, combinations of ORFs selected from ORFs 1 through

[32] 33 (SEQ ID NOS: 2 to [33] 34) are provided which are involved in the regulation of ramoplanin biosynthesis. In another embodiment, combinations of ORFs selected from ORFs 1 through [32] 33 (SEQ ID NOS: 2 to [33] 34) are provided which encode polypeptides that are involved in resistance and subcellular localization of the ramoplanin biosynthetic machinery. A single ORF or a combination of ORFs selected from ORFs 1 through [32] 33 (SEQ ID NOS: 2 to [33] 34) are provided to enhance production of ramoplanin by altering the expression level of an ORF selected from ORFs 1 through [32] 33 (SEQ ID NOS: 2 to [33] 34). In another embodiment, the expression level of an ORF selected from ORFs 1 through [32] 33 (SEQ ID NOS: 2 to [33] 34) may be altered to increase the yield of a particular form of ramoplanin.--

Please replace the paragraph beginning at page 10, line 30 with the following replacement paragraph:

--Ramoplanins are naturally produced by the microorganism *Actinoplanes sp.* ATCC 33076. The genetic locus encoding the biosynthetic pathway for ramoplanin production was isolated and cloned by the procedure described in USSN 09/910,813, from genomic DNA isolated from a ramoplanin producing strain of *Actinoplanes sp.* ATCC 33076 (obtained from the American Type Culture Collection, Manassas, VA, USA). This newly discovered locus encodes [32] 33 individual proteins involved in the biosynthesis of ramoplanin by this organism. The [32] 33 proteins are encoded by ORFs contained within the contiguous sequence of 88421 base pairs of DNA (SEQ ID NO: 1).--